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TITLE PAGE

Title

Long-term psychological distress in breast cancer survivors and their matched controls: a cross-sectional study

Running title

Long-term distress in breast cancer survivors

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ABSTRACT

Introduction

Breast cancer survivors often experience psychological distress shortly after diagnosis. Long-term psychological effects, however, have not been clearly demonstrated.

Methods

This cross-sectional cohort study included 350 breast cancer survivors and 350 age and general practitioner matched women. The median follow-up was 10 years. We compared with logistic regression, breast cancer survivors to controls on having (severe) symptoms of depression and/or anxiety, as measured with the Hospital Anxiety and Depression Scale. In multivariable logistic regression, we adjusted the results for a history of depression or prescription of antidepressants.

Results

Breast cancer survivors experienced more often symptoms of depression (10.6%) compared to controls (4.9%) and symptoms of anxiety (18.6%) compared to controls (16.3%). The odds of symptoms of depression (OR 2.3, 95%CI 1.3-4.2), severe symptoms of depression (OR 3.3, 95%CI 1.1-10.3) and severe symptoms of anxiety (OR 2.1, 95%CI, 1.1-4.0) were significantly higher for breast cancer survivors in comparison to the controls, even after adjusting for history of depression or prescription of antidepressants. No significant difference was seen for mild symptoms of anxiety.

Conclusions

Breast cancer survivors have an increased odds of experiencing (severe) symptoms of depression and severe symptoms of anxiety compared to controls, for up to at least 10 years after diagnosis.

Clinical Trial Registration at clinicaltrials.gov [ID:NCT01904331]

Keywords: Breast Neoplasms; Cross-Sectional Studies; Long Term Adverse Effects; Survivors; Primary Health Care; Depression; Anxiety.

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Highlights

- In our study, a large proportion of BC survivors did not experience symptoms of depression or anxiety.
- Long-term BC survivors are at increased odds of (severe) symptoms of depression
- Long-term BC survivors are at increased odds of severe symptoms of anxiety
- The increased odds are independent of a history of depression or antidepressants
- The increased odds are independent of time since BC diagnosis
- These increased odds seem to persist at least 10 years after BC diagnosis

1. INTRODUCTION

Breast cancer is the most common cancer in women^{1,2}. Fortunately, the survival of breast cancer has improved due to better screening and better treatments³. Numbers from the Netherlands show a 5-year survival rate of up to 88%⁴. Hence, the number of breast cancer survivors is also increasing.

The diagnosis of cancer and its treatment can have a great impact on a patient's psychological well-being⁵⁻⁸. However, both the clinicians and the patients may not be aware of possible long-term psychological impact and patients may not receive the proper support. No long-term follow up data are available with respect to the occurrence of psychological distress in breast cancer patients⁹. Therefore, it is important to know how prevalent long-term psychological distress is among breast cancer survivors. For women with breast cancer, this impact is mainly studied in the first five years after diagnosis when they still have follow-up controls with their oncologists¹⁰. In this period, Burgess et al. found a prevalence of 48% for depression, anxiety, or both for breast cancer survivors.¹¹ Which, they said, is twice as high as in the general female population. A recent systematic review of studies (2015) on symptoms of depression and anxiety among breast cancer survivors showed a widely distributed prevalence of 9.4-66.1% and 17.9-33.3%, respectively¹⁰. A few of the studies included women beyond the five years after diagnosis, and only two focused solely on women five years or more after their diagnosis of breast cancer^{12, 13}. One of these two found that 13% of women experienced severe symptoms of depression¹². However, they did not have a control population to evaluate if this proportion is more than on average. The other study evaluated women 5, 10 or 15 years after breast cancer diagnosis on quality of life and found that they had a higher score on symptoms of anxiety than random control women¹³. Unfortunately, the patient group and the control group significantly differed on age, environment (urban/rural) and income, which might have had an influence on the comparability on psychological well-being. Studies after 2015 have only been performed within the first years of diagnosis or in a hospital setting^{14, 15}.

For clinicians, survivors, and future guidelines, it is important to know if psychological distress is more prevalent among long-term breast cancer survivors than among women without cancer, in order to provide sufficient long-term support. Therefore in this study, we assessed symptoms of depression and anxiety at least five years after the diagnosis of breast cancer and compared with the results of women without a history of cancer, who were of the same age and general practitioner (GP).

2. METHODS

2.1 Context

In the Netherlands, all citizens are registered with a GP in their own residential area¹⁶. These GPs use electronic patient registers with coding systems of diagnosis (International Classification for Primary Care, ICPC) and medication prescriptions (Anatomical Therapeutic Chemical classification system, ATC)^{17, 18}. GPs are gatekeepers to secondary healthcare, which means that patients have to be referred by their GPs to medical specialists.

2.2 BLOC study design

Data for this study was derived from the Breast cancer Long-term Outcome of Cardiac dysfunction (BLOC)-study¹⁹. The primary outcome of the BLOC-study was the prevalence of long-term systolic and diastolic cardiac dysfunction among breast cancer survivors in comparison to matched controls. This cross-sectional cohort included 350 breast cancer survivors treated with chemo- and/or radiotherapy at least five years ago, and 350 randomly selected women from the same age and GP from the Northern part of the Netherlands (Supplementary Figure 1), recruited from 80 GPs. The control was randomly selected from the same GP database, from all women of the same age (+/- 1 year) as the breast cancer survivor. Exclusion criteria for the control were a history of cancer or cancer treatment. In both groups, women were excluded if they were not able to come to the university hospital according to their GP due to severe mental or physical illness. At the time of the cross-sectional assessment, the GP files of both breast cancer survivors and controls were searched for the code P76 and the date of the first diagnosis of depression was extracted. Furthermore, the first prescriptions of antidepressants (ATC-code N06A), anxiolytics (ATC-code N05B), and hypnotics and sedatives (ATC-code N05C) were analysed. Since the antidepressant amitriptyline can also be prescribed as an analgesic, it was excluded when prescribed for pain. The date of diagnosis of women with breast cancer functioned as the index date for the matched women. Therefore, the time since diagnosis for the control group is the time since the index date. The median age at the time of breast cancer diagnosis was 51 years (inter-quartile range [IQR] 45-57). The median follow-up was 10 years (IQR 7-14) years. The study is registered at clinicaltrials.gov [ID:NCT01904331]. The medical ethics committee of the University Medical Center Groningen (UMCG) approved this study, and all participants gave written informed consent. The study was performed in accordance with the Declaration of Helsinki.

2.3 Current study end-points

The primary outcome was the prevalence of (severe) symptoms of depression and/or anxiety as measured by the Hospital Anxiety and Depression Scale (HADS)²⁰. This questionnaire measures symptoms of both depression (HADS-D) and anxiety (HADS-A). It is a self-reported scale with 14 items scoring each 0-3, with a maximum score of 21 for either symptoms of depression or anxiety. Cut-off values are ≥ 8 for mild symptoms of depression/anxiety and ≥ 11 for severe symptoms of depression/anxiety. The HADS has been validated for both the general population and the breast cancer population^{21, 22}. The secondary outcomes were the prevalence of a

diagnosis of depression as registered by GPs after the diagnosis of breast cancer and/or a prescription of antidepressants after breast cancer diagnosis.

2.4 Statistical analyses

In the analysis, a diagnosis of depression and/or prescription of an antidepressant could be a determinant as well as an outcome. Survivors and controls with the first diagnosis of depression and/or first prescription of an antidepressant *before* the date of breast cancer diagnosis were considered as having a 'history of depression'. It is important to adjust for a history of depression, since depression is often a recurrent diagnosis. Survivors and controls with the first diagnosis of depression and/or first prescription of an antidepressant *after* the date of breast cancer diagnosis were considered as having an 'outcome of depression'. The diagnosis of depression and prescription of antidepressants were combined since some GPs may have the tendency to prescribe antidepressants for depression without coding a diagnosis of depression.

Table 1 describes participants' characteristics at the time of breast cancer diagnosis, including the number of survivors with a history of depression and the use of psychotropic medication before the date of breast cancer diagnosis. In table 2, the outcomes are described. For future comparability with other studies, both the continued and dichotomous values of the HADS are reported and tested with the Mann-Whitney U test.

In univariate logistic regression analyses, breast cancer survivors were compared to controls on the odds of having (severe) symptoms of depression and (severe) symptoms of anxiety as scored with the HADS, and on having diagnosis of depression and/or first prescription of an antidepressant *after* the date of breast cancer diagnosis (Table 2). In this way, odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated. To adjust for having a history of depression, multivariable logistic regression analyses were performed by adding this variable (Table 3 and 4). Data is presented stratified for depression and anxiety. In univariate logistic regression analyses the time since diagnosis for breast cancer survivors with increased HADS-scores were compared to the time since diagnosis for other breast cancer survivors.

To visualize the effect of time since follow-up, a graphical overview of the course of symptoms of depression and anxiety over time was constructed. The percentage of breast cancer survivors with an increased score on the HADS was compared to the percentage of controls, grouped by time since diagnosis, per two years. The minimum of women per time-subgroup had to be 20. All analyses were performed with the use of IBM SPSS statistics 23.

3. RESULTS

No significant differences were found between breast cancer survivors or controls regarding patient and therapy characteristics (Table 1)¹⁹. Only a prescription of hypnotics/sedatives before breast cancer diagnosis was significantly higher among controls compared to breast cancer survivors, respectively 9.4% and 3.7%.

All women completed the HADS questionnaire at the time of inclusion (median 10 years after breast cancer diagnosis). At this time 3.7% of breast cancer survivors experienced severe symptoms of depression compared to 1.1% of controls; a significant difference OR 3.3 (95%CI, 1.1-10.3). Concerning severe symptoms of anxiety, there was a significant difference between breast cancer survivors (8%) compared to controls (4%; OR 2.1 [95%CI, 1.1-4.0]), (Table 2).

The proportion of women with mild symptoms of depression was significantly higher for breast cancer survivors compared to controls (10.6% versus 4.9%; OR 2.3 [95%CI, 1.3-4.2]). For mild symptoms of anxiety, the difference was not significant 18.6% versus 16.3%; OR 1.2 [95%CI, 0.8-1.7]).

The answer to the HADS-D question 'I feel as if I am slowed down' showed the largest difference; 20.3% of BC survivors responded very often/almost-all-the time compared to 9.5% of the controls.

No significant differences were seen between breast cancer survivors and controls when comparing the continuous score on the HADS-D or HADS-A, p-values 0.197 and 0.056, respectively. After the diagnosis of breast cancer, no differences were seen in the registration of GPs concerning the diagnoses of depression or prescription of medication.

3.1 Multivariable analysis

After adjusting history of depression as registered by the GPs before the date of breast cancer, all odds were significantly higher for breast cancer survivors compared to controls: severe symptoms of depression (HADS-D \geq 11; OR 3.3 [95%CI 1.1-10.3]), severe symptoms of anxiety (HADS-A \geq 11; OR 2.1 [95%CI 1.1-4.1]), mild symptoms of depression (HADS-D \geq 8; OR 2.3 [95%CI 1.3-4.2]) and mild symptoms of anxiety (OR 2.1 [95%CI 1.1-3.2]). This is shown in table 3.

3.2 Time since diagnosis

Time since diagnosis was not associated with symptoms of (severe) depression or anxiety among breast cancer survivors. The figures visualize the proportion of women (breast cancer survivors and controls) with (severe) symptoms of depression (Figure 1) or anxiety (Figure 2) with a specific follow-up duration. The proportion of women with severe or mild symptoms of depression and severe symptoms of anxiety is higher among the breast cancer survivors than among the controls for every time-subgroup.

4. DISCUSSION

To our knowledge, no other study included women at least five years after breast cancer diagnosis from the general population and compared their symptoms of depression and anxiety with women of the same age without any cancer. When discussing the findings, it is important to realize that a large proportion of the long-term breast cancer survivors in our study did not experience symptoms of depression or anxiety (89.4% and 81.4%, respectively) at the moment of measurement. This does not exclude the possibility that they have experienced symptoms of depression or anxiety at an earlier stage, that might have recovered since then.

4.1 Assessing proportions of symptoms

There is some discrepancy in literature regarding the proportions of breast cancer survivors with symptoms of depression and anxiety¹⁰. Some studies report comparable results, were others report different figures^{12, 23, 24}. The prevalence of women with symptoms of depression and anxiety found in this study is low in comparison to other studies^{25, 26}. The main explanations for these differences are the differences in follow-up time, differences in age of the included women, and the differences in applied questionnaires. The controls from our study had a lower proportion of women with severe symptoms of depression or anxiety compared to a European female population²⁷. However, these proportions were within the confidence intervals of our control population: 2.9% severe symptoms of depression and 10.0% severe symptoms of anxiety, respectively. The European population was selected at random and might have included women with (a history of) cancer. In addition, the difference might be due to the younger age of the participants in the European population, which is associated with an increased score on the HADS questionnaire for symptoms of depression and anxiety²⁸⁻³⁰.

4.2 Comparison symptoms with controls

We found an increased odds of severe symptoms of depression and anxiety among long-term breast cancer survivors compared to controls. The mean scores in this study did not significantly differ. Claus et al. found significant higher mean scores for severe symptoms of depression among breast cancer survivors than among controls, measured with the CES-D questionnaire (mean follow-up 5.8 years)³¹. Klein et al. compared mean scores for severe symptoms of anxiety among long-term breast cancer survivors and controls and found significantly higher mean scores for survivors, measured with the STAI questionnaire (5, 10 or 15 years after breast cancer diagnosis)¹³.

We found an increased odds of mild symptoms of depression among long-term breast cancer survivors compared to controls. None of the studies compared mild symptoms of depression or anxiety among breast cancer survivors and controls. Hoffman et al. evaluated psychological distress in a long-term cancer survivors cohort (22.9% breast cancer, ≥5 years after diagnosis) and found significantly more psychological distress among cancer survivors than among controls without cancer, measured with the self-reporting K6 scale, designed to assess nonspecific psychological distress³².

4.3 History of depression

A previous diagnosis of depression or prescription of antidepressants before the cancer diagnosis had no effect on the odds of having (severe) symptoms of depression or severe symptoms of anxiety for breast cancer survivors in comparison to controls in our population. In contrast, other research defined a history of depression as a risk factor for depression after breast cancer, but in that study the outcome measure was a diagnosis of depression and not symptoms of depression¹¹. Interestingly, in our study all women (survivors and controls) with a history of depression had significantly more mild symptoms of anxiety. One could hypothesize that women with a history of depression are more anxious than others, perhaps by nature or they might fear recurrence of psychological distress. However, this was not the aim of this study and not evaluated further.

4.4 Time since diagnosis

Time since diagnosis was not associated with having (severe) symptoms of depression and severe symptoms of anxiety for breast cancer survivors. These results are in-line with the results of another study among survivors two to ten years after diagnosis³³. Additionally, in a large long-term cancer survivors cohort more than five years after cancer diagnosis, no association was found with time since diagnosis³². A significant difference of symptoms of depression one year after diagnosis compared to women in the general population appeared to decline in the following years¹⁰. A complete decline was not supported by the results of our study, as the time since diagnosis had no significant effect on the elevated odds of breast cancer survivors having symptoms of depression.

4.5 Strengths and limitations

The main strength of this study is that we have included a random sample of women from the general population. Although no other study included this unselected population, it can be argued that our population still does not include the mean breast cancer patient. Which is true, because the included patients were slightly younger and a higher percentage received radiotherapy. Therefore, we might underestimate the occurrence of anxiety and depression. Also, breast cancer survivors are more likely to be underdiagnosed than controls, because signs of depression or anxiety might be interpreted as “natural” consequences of cancer⁷. The median follow-up of 10 years is a strength, because it focusses exclusively on the long-term effects. In order to achieve a uniform outcome, we let all the participants complete the HADS questionnaire, hereby relying on the symptoms the women are experiencing at that point in time, rather than on patients’ help-seeking or doctors’ coding behaviour. It is important to realize that the HADS questionnaire only measures symptoms of depression; for an actual diagnosis of depression a clinical interview has to be performed. However, the HADS-D and HADS-A have a sensitivity and specificity of approximately 0.80 for depression and anxiety³⁴. Furthermore, we adjusted for a history of depression before breast cancer as registered by GPs to ensure that an already psychologically delicate group did not influence the results. In both groups, women with depression or depressive symptoms might be less inclined to participate, making the comparison equal. Missing from our data is the diagnosis of anxiety disorder; unfortunately, this data was not retrieved from the GP databases. Notable, controls had more

prescriptions of hypnotics/sedatives at the time of breast cancer diagnosis than the breast cancer survivors. However, the effect on the results is expected to be minimal since the number was comparable at the time of cross-sectional assessment. It should be taken into account that socioeconomic (SES), occupational and marital status were not assessed in this study.

4.6 Conclusion

At least five years after breast cancer, breast cancer survivors have a higher prevalence of (severe) symptoms of depression and severe symptoms of anxiety, even after adjusting for a history of depression prior to breast cancer. Future studies should take into account factors such as fatigue and SES. However, in our study more than 80% of long-term breast cancer survivors did not have mild or severe symptoms of depression or anxiety.

Conflict of interest statement

None of the authors had any potential conflicts of interest.

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FIGURE LEGENDS

Figure 1. Percentage of breast cancer survivors and controls with symptoms of depression, per two years after breast cancer diagnosis.*

* Since the minimum of women per time-subgroup was 20, the subgroup goes up to 13-14 years after breast cancer diagnosis.

Figure 2. Percentage of breast cancer survivors and controls with symptoms of anxiety, per two years after breast cancer diagnosis.*

* Since the minimum of women per time-subgroup was 20, the subgroup goes up to 13-14 years after breast cancer diagnosis.

TABLES

Table 1: At the time of breast cancer diagnosis or index date^a: Characteristics of breast cancer survivors and matched controls.

	Breast cancer survivors (N = 350) ^b	Controls (N = 350) ^b
Age at breast cancer diagnosis or index date for matched control; years, median (IQR)	51 (45-57)	51 (45-57)
	N (%)	N (%)
<i>Breast cancer treatment as registered in the hospital and general practitioners files</i>		
Chemotherapy	175 (50.0)	
<i>Anthracycline-based</i>	142 (81.1)	–
<i>Cumulative anthracycline dose; mg/m², median (IQR)^c</i>	238 (228–240)	–
Trastuzumab	13 (3.7)	–
Anti-hormonal treatment	146 (41.7)	–
Radiotherapy	295 (84.3)	–
<i>Diagnosis of depression or prescriptions <u>before</u> the time of breast cancer diagnosis or index date for matched control^a</i>		
History of breast cancer: diagnosis of depression or antidepressants ^d	36 (10.3)	36 (10.3)
A diagnosis of depression ^d	14 (4.0)	21 (6.0)
A prescription of any antidepressants ^d	29 (8.3)	24 (6.9)
A prescription of anxiolytics ^d	39 (11.1)	37 (10.6)
A prescription of hypnotics or sedatives ^d	13 (3.7)	33 (9.4)

^a The date of breast cancer diagnosis from the survivor was made identical for the matched control (index date);

^b There were no statistically significant differences between groups, tested with Chi-square test or Mann-Whitney U test, except for a prescription of hypnotics or sedatives; numbers in bold means significant at p <0.05 level;

^c Doxorubicin isotoxic dose, information available for 108 survivors (76%);

^d Extracted from electronic patient files of general practitioners.

Table 2: At time of cross-sectional measurement: Univariate comparison of outcomes between breast cancer survivors and matched controls.

	Breast cancer survivors (N = 350)	Controls breast cancer survivors (N = 350)	
Follow-up duration ^a ; years, median (IQR)	10 (7-14)	10 (7-14)	
Age: years, median (IQR)	63 (57-68)	63 (57-68)	
	N (% , 95%CI)	N (% , 95%CI)	OR (95%CI) ^b
<i>Depression</i>			
HADS-Depression ^c			
HADS-D ≥ 8	37 (10.6, 7.3-13.9)	17 (4.9, 2.6-7.2)	2.3 (1.3-4.2)
HADS-D ≥ 11	13 (3.7, 1.7-5.7)	4 (1.1, 0.0-2.3)	3.3 (1.1-10.3)
Continuous median (IQR) ^d	2 (1-4)	2 (1-4)	0.197
<i>Anxiety</i>			
HADS-Anxiety ^c			
HADS-A ≥ 8	65 (18.6, 14.4-22.7)	57 (16.3, 12.3-20.2)	1.2 (0.8-1.7)
HADS-A ≥ 11	28 (8.0, 5.1-10.9)	14 (4.0, 1.9-6.1)	2.1 (1.1-4.0)
Continuous median (IQR) ^d	5 (3-7)	4 (3-6)	0.056
<i>Diagnosis of depression or prescriptions <u>after</u> time of breast cancer diagnosis or index date for matched control^a</i>			
First diagnosis of depression ^e	18 (5.1, 2.8-7.5)	13 (3.7, 1.7-5.7)	1.4 (0.7-2.9)
First prescription of any antidepressant ^e	41 (11.7, 8.3-15.2)	39 (11.1, 7.8-14.5)	1.1 (0.7-1.7)
First prescription of any anxiolytics ^e	46 (13.1, 9.5-16.8)	49 (14.0, 10.3-17.7)	0.9 (0.6-1.4)
First prescription of any hypnotics or sedative ^e	41 (11.7, 8.3-15.2)	34 (9.7, 6.5-12.9)	1.2 (0.8-2.0)

^a The date of breast cancer diagnosis from the survivor was made identical for the matched control (index date);

^b Numbers in bold means significant at p <0.05 level;

^c Explanation: HADS ≥ 8 = Symptoms of mild depression (HADS-D) or anxiety (HADS-A) and HADS ≥ 11 = symptoms of severe depression (HADS-D) or anxiety (HADS-A);

^d Tested with Mann-Whitney U test;

^e Extracted from electronic patient files of general practitioners.

Table 3: Regression analyses: Comparison of outcomes at the time of cross-sectional measurement from the Hospital Anxiety Depression Scale (HADS) - Depression and Anxiety, between breast cancer survivors and matched controls.

		HADS-D $\geq 8^a$	HADS-D $\geq 11^a$	HADS-A $\geq 8^a$	HADS-A $\geq 11^a$
		OR (95%CI) ^b	OR (95%CI) ^b	OR (95%CI) ^b	OR (95%CI) ^b
<i>Univariate regression analyses</i>					
History of breast cancer	No	1	1	1	1
	Yes	2.3 (1.3-4.2)	3.3 (1.1-10.3)	1.2 (0.8-1.7)	2.1 (1.1-4.0)
History of depression ^c	No	1	1	1	1
	Yes	1.3 (0.6-2.1)	1.9 (0.5-6.8)	1.8 (1.0-3.2)	2.2 (0.97-4.9)
<i>Multivariable regression analyses (adjusted for each other)</i>					
History of breast cancer	No	1	1	1	1
	Yes	2.3 (1.3-4.2)	3.3 (1.1-10.3)	1.2 (0.8-1.7)	2.1 (1.1-4.1)
History of depression ^c	No	1	1	1	1
	Yes	1.3 (0.6-3.1)	1.9 (0.5-6.9)	1.8 (1.0-3.2)	2.2 (0.97-5.0)

^aExplanation: HADS-D (Depression) ≥ 8 = mild symptoms of depression and HADS-D ≥ 11 = severe symptoms of depression, HADS-A (Anxiety) ≥ 8 = mild symptoms of anxiety and HADS-A ≥ 11 = severe symptoms of anxiety;

^bNumbers in bold means significant at $p < 0.05$ level;

^cThe determinant 'history of depression' was defined as a diagnosis of depression and/or prescription of an antidepressant before the date of breast cancer diagnosis or index date;

SUPPLEMENTARY INFORMATION

Supplementary figure 1. Design of the study.